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(54) Title: 7-AMINO-2-HEPTENOATES AND THEIR USE IN THE PREPARATION OF METHYLPHENIDATE

(57) Abstract

Novel compounds are of the formula Y^1Y^2N-$(CH_2)_4$-CH=C(Ph)-X wherein Y^1 and Y^2 are independently H or a removable blocking group, or Y^1 and Y^2 together are a removable divalent blocking group; and X is $COOCH_3$ or a group convertible thereto. Such a compound may be cyclised, by Michael addition, to give methylphenidate, if necessary after removing blocking group(s) and converting X to $COOCH_3$.

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7-AMINO-2-HEPTENOATES AND THEIR USE IN THE PREPARATION OF METHYLPHENIDATE

Field of the Invention

This invention relates to the synthesis of methylphenidate by cyclisation of new 7-amino-2-heptenoates.

Background of the Invention

Methylphenidate has utility as a therapeutic agent, e.g. in the treatment of attention-deficient hyperactivity disorder. It was first prepared as a mixture of the *erythro* and *threo* racemates. US-A-2957880 discloses its synthesis and also studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereomer.

JP-A-53007627 discloses the formula

$$R^*\text{-}NH\text{-}(CH_2)_4\text{-}CH{=}CH\text{-}COOR$$

wherein R* is the chiral auxiliary α-methylbenzylamine and R is lower alkyl. This structure is indicated as suitable for cyclisation to 1-(1-phenylethyl)-2-hydroxy-5-piperidinone, en route to antihistaminic agents.

No cyclisation is demonstrated. Further, the elemental analysis of the compound that is made, consistent with the intended product, indicates that it is actually of the formula

$$R^*\text{-}NH\text{-}CO\text{-}(CH_2)_3\text{-}CH{=}CH\text{-}COOR$$

The fact that this is an amide may account for failure of the proposed cyclisation.

Knouzi *et al*, Tet. Lett. 28(16):1757-60 (1987), disclose cyclisation, again by Michael addition, of 7-amino-2-heptenoates of the formula

$$H_2N\text{-}(CH_2)_4\text{-}CH{=}CR''\text{-}COOCH_3$$

wherein R" is H or CH_3. The resultant piperidines, and also analogous compounds, were obtained with good diastereoselectivity, except for the given compound when R" is CH_3.

Summary of the Invention

The present invention is based on the realisation that compounds of formula I

$$Y^1Y^2N\text{-}(CH_2)_4\text{-}CH{=}CPh\text{-}X \qquad (I)$$

wherein Y^1 and Y^2 are independently H or a removable blocking group, or Y^1 and Y^2 together are a removable divalent blocking group, and X is $COOCH_3$ or a group

convertible thereto, are novel intermediates that provide the basis of a new synthesis of methylphenidate. Further, cyclisation by Michael addition proceeds substantially only on one of the two geometric isomers. Thus, contrary to the most closely analogous situation in the prior art, effective and useful diastereoselectivity is found.

Therefore, according to a further aspect of this invention, compounds of formula I when Y^2 is H can be converted to methylphenidate by Michael addition, using a base such as lithium diethylamine, removing any blocking group represented by Y^1, and converting X to $COOCH_3$, if necessary.

According to yet another aspect of the invention, compounds of formula I may be prepared by a Horner-Wadsworth-Emmons reaction of corresponding compounds of the formulae Ph-CHX-PO(Oalk)$_2$ and Y^1Y^2N-$(CH_2)_4$-CHO, wherein Y^2 is a blocking group; and, if desired, removing the blocking group to give the product in which Y^2 is H.

Description of the Invention

X is preferably $COOCH_3$. Alternatively, it may be CN, $CONH_2$ or $COOR^1$, R^1 being H or alkyl or aralkyl of up to 10 C atoms. Other groups X that can readily be converted to $COOCH_3$, and methods of conversion, will be readily apparent to one of ordinary skill in the art.

Y^1 and Y^2 may each be H. Either or each, or the two together, may also be a blocking group. Groups that can readily be introduced onto a N atom, and readily removed after another part of the molecule has undergone reaction, are well known to those of ordinary skill in the art. For example, reference may be made to T.W. Greene *et al*, "Protecting Groups in Organic Synthesis", 2nd ed. Wiley-Interscience, New York (1991). A particular example of a suitable blocking group is t-butyloxycarbonyl (Boc). An example of Y^1 and Y^2 together with N is phthalimido.

In certain circumstances, it may be preferred that Y^1 is a chiral auxiliary, in single enantiomer form. A preferred example is 1-phenylethyl, which may be introduced using, say, α-methylbenzylamine (α-MBA), and removed by hydrogenation. The use of a chiral auxiliary may assist control of absolute and/or relative stereochemistry. Either enantiomer may be used, depending on the desired product, and this may readily be determined by experiment. Any *erythro* diastereoisomer formed by cyclisation may be

subjected to epimerisation at the benzylic position to give optically-enriched *threo* methylphenidate or a derivative thereof.

Each of the reactions described herein may be conducted by generally known methodology, and any variations that may be necessary for optimisation can readily be determined by one of ordinary skill in the art. Any desired resolution, e.g. to obtain *d-threo*-methylphenidate, may be conducted by known means. Preferred resolution processes are described in PCT/GB97/00185 and PCT/GB97/00643. Such resolutions may be combined with the racemisation described in PCT/GB97/00281. The contents of these copending Applications are incorporated herein by reference.

Scheme 1 illustrates a synthesis of a racemic compound of formula I. Scheme 2 illustrates a synthesis of optically pure compound of formula I, starting from glutaric anhydride and optically-pure α-MBA. The four steps of Scheme 1 are further illustrated by the following Examples 1 to 4, respectively. Example 5 illustrates the cyclisation by Michael addition.

Example 1

5-Amino-1-pentanol (30.0 g, 0.29 mol) and acetophenone (34.9 g, 0.29 mol) were condensed by refluxing in toluene (100 ml) under Dean and Stark conditions in the presence of 1% $ZnCl_2$ (20 mg). Toluene was removed and substituted with MeOH (100 ml), and then $NaBH_4$ (10.8 g, 0.29 mol) was added to reduce the imine. MeOH was removed and the product was partitioned between EtOAc (150 ml) and water (150 ml). After aqueous workup, the amine was obtained as a yellow oil (51 g, 85%).

Example 2

The secondary amine was protected by a Boc group. The amine (38.0 g, 18 mol) was treated with 1 eq Boc_2O (39.9 g, 0.18 mol) in a biphasic mixture of THF/2M NaOH (200 ml) for 2 hrs. The product was chromatographed on silica using EtOAc/heptane 1:1 to afford the Boc-protected amide (50.0 g, 89%).

Example 3

The alcohol (17.0 g, 0.55 mol) was oxidised to the aldehyde using standard conditions (DMSO-oxalyl chloride-TEA) (3:1.5:7 in DCM). The crude product was chromatographed through silica with EtOAc/heptane 2:8, to afford the aldehyde as a yellow oil (11.52 g, 68%).

Example 4

Methyl (+)-2-bromophenylacetate (51.14 g, 96%) was prepared from the free acid (50.0 g, 0.23 mol) in 96% yield with 1 eq of acetyl chloride (18.3 g, 16.5 ml) in methanol (20 ml) at room temperature. Triethyl phosphite (12.35 ml, 0.72 mol) was added over a period of 20 minutes to methyl α-bromophenyl acetate (15.0 g, 0.65 mol) at 120°C, and then the mixture was heated for 3 hrs at 160°C. The phosphonate was isolated cleanly in quantitative yield (19.5 g, 100%).

1 M $(Me_3Si)NNa$ (4.9 ml) was added to a solution of the phosphonate (1.4 g, 4.91 mmol) in THF (5 ml) at -78°C. A solution of the aldehyde (1.0 g, 3.27 mmol) in THF (5 ml) was added dropwise. The solution was warmed to room temperature overnight. After aqueous workup, a 1:1 mixture of the geometric isomers of formula I was obtained (0.89 g; 66%).

Treatment of the Boc-protected amino-alkene (0.89 g, 2.0 mmol) with neat TFA (2 ml) cleanly removed the Boc group. The trifluoroacetate salt was treated with TEA (2 ml) in MTBE (5 ml). Surprisingly, the free amine was isolated rather than the cyclised product (0.69 g; 101%).

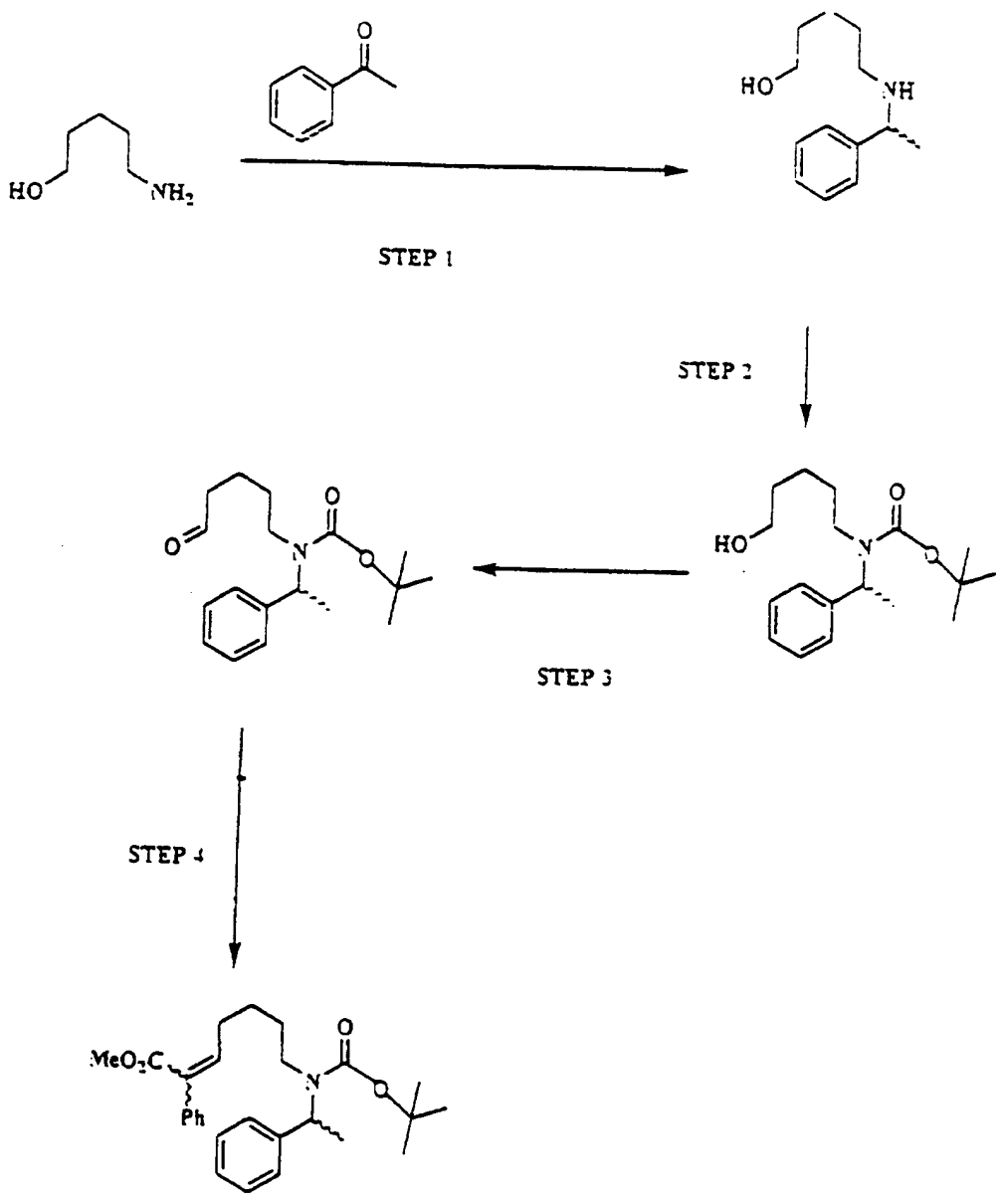
Example 5

A dilute solution of the free amine (0.66 g, 1.98 mmol) in THF (10 ml) was added dropwise to freshly prepared 0.28 MLDA (8.5 ml, 2.38 mmol) in THF (50 ml) at -78°C. The mixture was then warmed to -20°C over 2 h, before being quenched with saturated ammonium chloride.

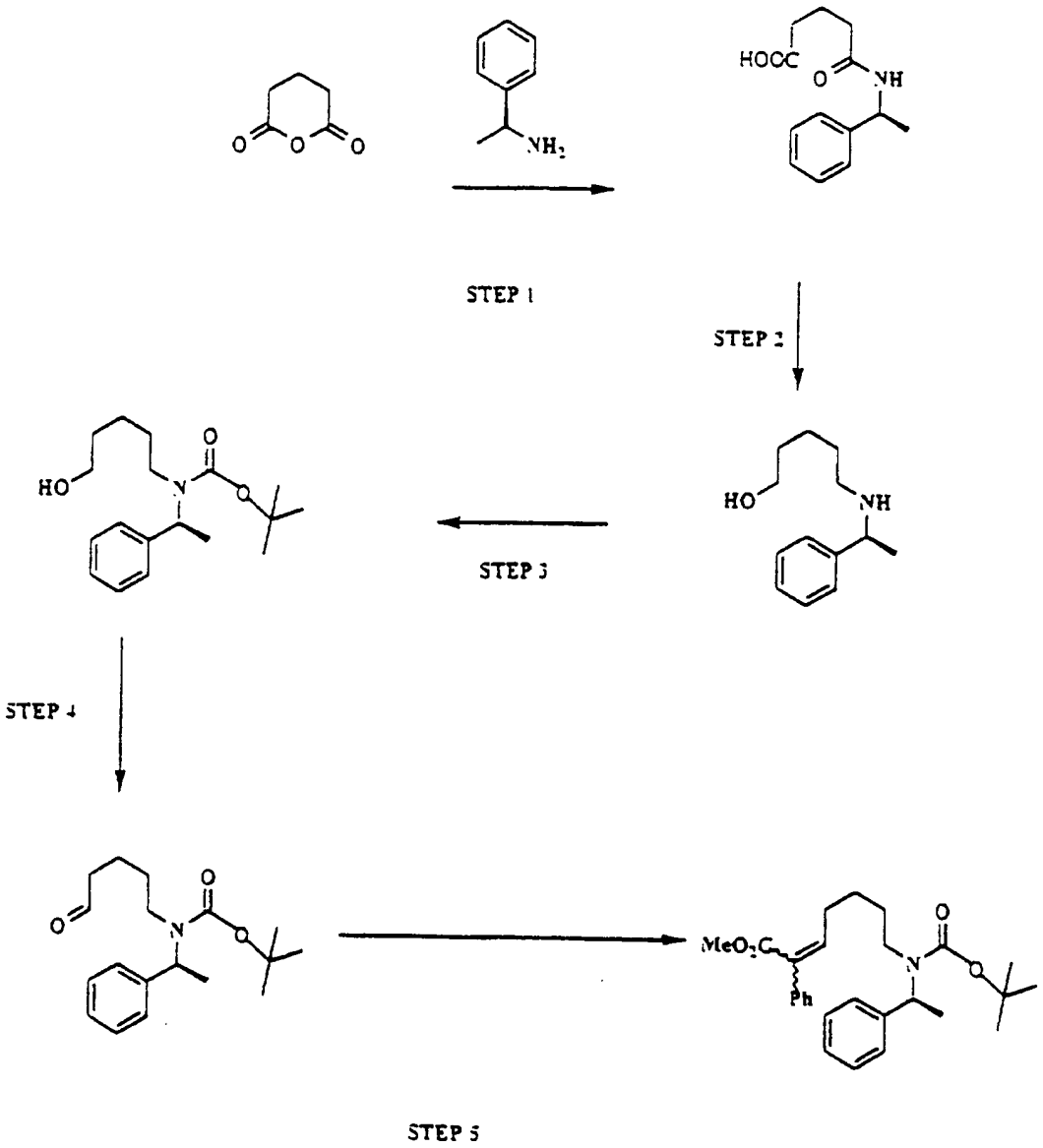
The ^1H NMR spectrum of the crude product showed that one geometric isomer of the starting material had not reacted while the other isomer had undergone a Michael addition. Column chromatography of the product mixture gave a single geometric isomer of unreacted amine and the cyclised product.

The sample of cyclised material is not completely pure, but the ^1H NMR spectrum indicates that 2:1 mixture of major diastereomers has been produced. In theory, four diastereomers could be produced in this reaction, therefore there is good diastereoselectivity.

Scheme 1



Scheme 2



CLAIMS

1. A compound of the formula

$$Y^1Y^2N\text{-}(CH_2)_4\text{-}CH{=}C(Ph)\text{-}X$$

wherein Y^1 and Y^2 are independently H or a removable blocking group, or Y^1 and Y^2 together are a removable divalent blocking group; and X is $COOCH_3$ or a group convertible thereto.

2. A compound according to claim 1, wherein X is CN, $CONH_2$ or $COOR^1$, R^1 being H or alkyl or aralkyl of up to 10 C atoms.

3. A compound according to claim 1 or claim 2, wherein Y^1 is H or a chiral auxiliary.

4. A compound according to any preceding claim, wherein Y^1 is 1-phenylethyl.

5. A compound according to claim 3 or claim 4, wherein Y^2 is H.

6. A process for preparing a compound according to any preceding claim, which comprises a Horner-Wadsworth-Emmons reaction of corresponding compounds of the formulae $Ph\text{-}CHX\text{-}PO(Oalk)_2$ and $Y^1Y^2N\text{-}(CH_2)_4\text{-}CHO$, wherein Y^2 is a blocking group; and, if desired, removing the blocking group to give the product in which Y^2 is H.

7. A process for preparing methylphenidate, which comprises a Michael reaction, using base, on a compound according to claim 5; removing any blocking group represented by Y^1; and, if X is not $COOCH_3$, converting it to $COOCH_3$.

8. A process according to claim 7, wherein the base is lithium diethylamine.

9. A process according to claim 7 or claim 8, wherein Y^1 is 1-phenylethyl and it is removed by hydrogenation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00811

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/34 C07C227/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 002, no. 048 (C-010), 31 March 1978 & JP 53 007627 A (TEIJIN LTD), 24 January 1978, cited in the application see abstract ---	1,6
A	US 2 957 880 A (RUDOLF ROMETSCH) 25 October 1960 cited in the application see the whole document --- -/--	7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	TETRAHEDRON LETTERS, vol. 28, no. 16, 1987, OXFORD GB, pages 1757-1760, XP002031799 N. KNOUZI ET AL.: "intramolecular cyclization ....." cited in the application see the whole document -----	1

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nformation on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2957880 A	25-10-60	NONE	